Received: 23 August 2021 | Revised: 1 February 2022 | Accepted: 6 February 2022

DOI: 10.1002/hsr2.563

ORIGINAL RESEARCH

Health Science Reports Open Access WILEY

Prospective randomized comparison of effect on coronary endothelial and renal function between febuxostat and benzbromarone in hyperuricemic patients with coronary artery disease: EFEF study

Masami Nishino | Yasuyuki Egami | Hitoshi Nakamura | Kohei Ukita | Akito Kawamura | Yutaka Matsuhiro | Koji Yasumoto | Masaki Tsuda | Akihiro Tanaka | Naotaka Okamoto | Yasuharu Matsunaga-Lee | Masamichi Yano | Ryu Shutta | Jun Tanouchi

Division of Cardiology, Osaka Rosai Hospital, Osaka, Japan

Correspondence
Masami Nishino, Division of Cardiology, Osaka Rosai Hospital, 1179-3, Nagasone-Cho, Sakai-City, Osaka 591-8025, Japan.
Email: mnishino@osakah.johas.go.jp

Abstract

Background and Aims: There are two types of serum uric acid-lowering agents, the xanthine oxidoreductase (XO) inhibitor and non-XO inhibitor. We investigated whether febuxostat, XO inhibitor, could produce more favorable effects on coronary endothelial function (CEF) and renal function than benzbromarone, non-XO inhibitor, in hyperuricemic coronary artery disease (CAD) patients.

Methods: We divided 21 hyperuricemic patients with stenting for left anterior descending (LAD) or left circumflex (LCX) artery into patients started on febuxostat (F group) and those on benzbromarone (B group). After 8 months, all patients underwent CEF evaluations (acetylcholine provocation test) and optical coherence tomography (OCT) for non-culprit vessels (e.g. if patients received LAD stenting, we evaluated LCX). We compared the diameter ratio induced by acetylcholine and baseline (CEF ratio), thin-cap fibroatheroma and calcified plaque by OCT, uric acid, oxidative stress biomarkers, and renal function including estimated glomerular filtration rate (eGFR) between F and B groups. Creatinine 2 days after stenting was measured to evaluate contrast-induced nephropathy (CIN).

Results: Change of eGFR was significantly lower in F group (n= 11) than B group over 8 months while the other parameters including CEF ratio were similar. F group showed favorable effects for CIN.

Conclusion: In conclusion, 8-months of febuxostat, XO inhibitor, does not significantly protect CEF but can protect the renal function including CIN in hyperuricemic patients with CAD compared to benzbromarone, non-XO inhibitor.

KEYWORDS

coronary artery disease, endothelial function, febuxostat, renal function, uric acid

1 | INTRODUCTION

It has been reported that hyperuricemia may contribute to the development and progression of cerebral and cardiovascular diseases, chronic kidney disease (CKD), and mortality.[1,2] However, the mechanism for why hyperuricaemia is correlated with cerebro-cardiovascular or renal disease is still unknown. There are two types of serum uric acid (SUA)-lowering agents, the xanthine oxidoreductase (XO) inhibitors including febuxostat, and uricosuric treatment without XO inhibition including benzbromarone. However, whether a high SUA level itself is actively correlated or XO activity is merely correlated with various arterial diseases has not been well investigated.[3] On the other hand, the debate is ongoing as to whether SUA-lowering agents can contribute to improving various arterial diseases including cerebro-cardiovascular disease and CKD.[4–6] However, there have been many studies indicating that SUA-lowering agents, especially XO inhibitors, have beneficial effects on a number of surrogate markers in hyperuricemia patients, such as endothelial dysfunction,[7] the peripheral blood flow,[8] hospitalizations,[9] and a metabolic imbalance.[10] Regarding endothelial dysfunction, almost all studies have used a flow-mediated dilatation (FMD) test.[7] In the present study, we focused on SUA-lowering agents for coronary endothelial function (CEF). Therefore, we estimated the CEF by measuring the coronary vasomotion in response to acetylcholine (ACh) because this method is a useful and reliable method to measure the CEF, but, this test is a little complicated and the rate of serious major complications using this test is 0.9%.[11]

On the other hand, although several reports have revealed the beneficial effect of febuxostat on renal protection,[4,5] there were little reports regarding the effect of febuxostat on contrast-induced nephropathy (CIN).

The aim of the present EFEF (effect of febuxostat on endothelial function) study was to investigate whether the XO inhibitor, febuxostat, has greater beneficial effects on the CEF than a uricosuric treatment without XO inhibition using benzbromarone, in asymptomatic hyperuricemic patients with coronary artery disease (CAD). In addition, we evaluated the effects of these drugs on renal function including CIN.

2 | METHODS

2.1 | Study protocol

From April 2016 to January 2018, consecutive hyperuricemic patients (SUA ≥ 6.0 mg/dl) with CAD who had severe stenosis of the left anterior descending (LAD) or left circumflex (LCX) artery and who in addition did not have significant stenosis (≥50% diameter stenosis) of the other left coronary artery (LCA) by initial coronary angiogram or coronary computed tomographic angiogram were prospectively enrolled in the EFEF study. The exclusion criteria were as follows: vasospastic angina (VSA), acute coronary syndrome, left main coronary artery stenosis, heart failure with reduced ejection fraction (EF) (left ventricular EF < 40%), hemodialysis, history of coronary artery bypass surgery, and history of the percutaneous coronary intervention (PCI). After providing written informed consent, eligible patients were randomly assigned to the patients who received febuxostat (Teijin Pharma) (initial dose of 10 mg daily that was titrated to 20 mg daily at 1 month and 40 mg daily at 2 months) (F group) and those who received benzbromarone (Towa Pharma) (100 mg/day) (B group) by the sealed envelope system.[12] The patients started to receive febuxostat or benzbromarone to treat hyperuricemia. Two weeks later, we performed PCI for the severe stenosis lesion. We implanted a drug-eluting stent (DES) by optical coherence tomography (OCT) or intravascular ultrasound (IVUS) guidance. Figure 1 summarizes the study schema. At the 8-month follow-up, all patients underwent a CEF evaluation by assessing the response to intracoronary ACh and an OCT evaluation for nonculprit vessels (e.g., if the patient received LAD stenting, we evaluated the LCX). Blood and urinary samplings were performed at baseline (before receiving febuxostat or benzbromarone) and at the 8-month follow-up. In addition, the creatinine was measured 2 days after PCI. During the study period, the patients continued to receive the same medications excluding febuxostat and benzbromarone. All patients received a detail informed consent and the Ethical Committee of Osaka Rosai Hospital approved this study.

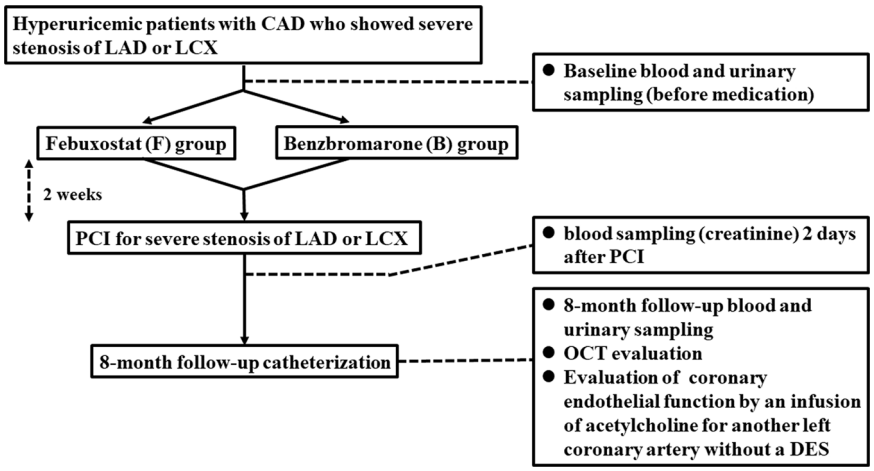

FIGURE 1 Patient flowchart. CAD, coronary artery disease; DES, drug-eluting stent; LAD, left anterior descending artery; LCX, left circumflex artery; OCT, optical coherence tomography; PCI, percutaneous coronary intervention

2.2 | Serum and urinary markers

To evaluate the drug effects on SUA, oxidative stress, inflammation, and renal protection, we measured the following biomarkers one day before stenting and at the 8-month follow-up: SUA, malondialdehyde-modified low-density lipoprotein (MDA-LDL), urinary 8-Hydroxy-2′-deoxyguanosine (8-OHdG), high-sensitive C-reactive protein (hs-CRP), creatinine, cystatin C, and estimated glomerular filtration rate (eGFR). The eGFR was determined using the estimation formula for Japanese.[13] To evaluate the CIN, we also measured the creatinine 2 days after PCI.[14]

2.3 | ACh provocation test to evaluate CEF

At the 8-month follow-up after DES implantation, we performed ACh provocation test. Intravenous heparin (50–70 units/kg) was administered, and a 5 French guiding catheter was used to engage the LCA. After the coronary angiography to evaluate the LCA, a bipolar electrode catheter was inserted into the right ventricular apex through the femoral vein or antecubital vein and was connected to a temporary pacemaker set at a rate of 45 beats/min. We tested the CEF by injecting intracoronary ACh, which was directly injected in incremental doses of 20, 50, and 100 μg into the LCA over 20 s, with at least a 3-min interval between injections unless there was significant bradycardia, atrioventricular block, paroxysmal atrial fibrillation, or severe vasoconstriction. After 1 min following the completion, coronary arteriography was performed. Finally, a 2.5–5.0 mg bolus of intracoronary isosorbide dinitrate (ISDN) was administered to evaluate the endothelium-independent vasodilation of the epicardial artery.[11] During the study, the arterial blood pressure and an electrocardiogram (ECG) were continuously monitored on an oscilloscope. A standard 12-lead ECG was recorded every 30 s. We also recorded the patient's symptoms, ischemic ECG changes, and complications/side effects if any, during the intracoronary ACh infusion.

2.4 | Quantitative coronary angiography (QCA)

Two experienced physicians, who did not know the clinical, physiological, or OCT data, performed the QCA on the nonstenting LCA using a computer-assisted method (CAASII; Pie Medical Imaging BV) to determine the minimum lumen dimension (MLD) at baseline, after each intracoronary ACh injection and after the intracoronary ISDN administration.

2.5 | Evaluation of CEF

The coronary angiograms at the maximally tolerated dose of ACh were later compared with the baseline coronary angiogram by QCA to evaluate CEF using the CEF ratio. The CEF ratio was defined as the ratio of the MLD induced by ACh and the lumen dimension at the same part at baseline, which was measured by QCA in the proximal to mid part of the non-stented LCA.[15] A representative case is shown in Figure 2. In this case, the patient received a DES in the LCX.

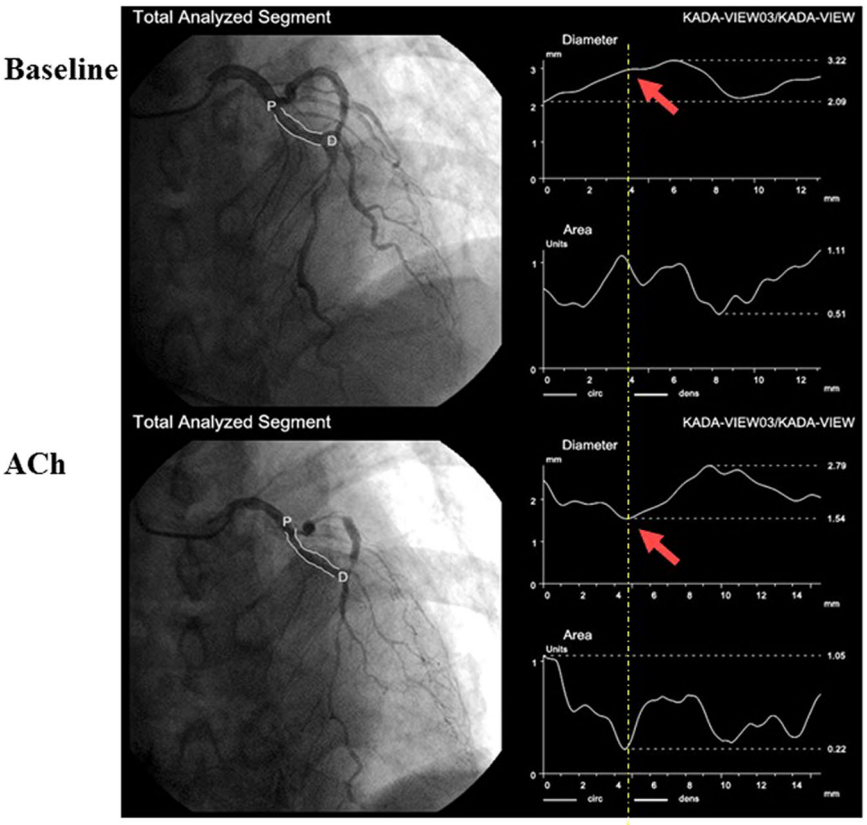

FIGURE 2 A representative case of acetylcholine (ACh) provocation test. This patient received a drug-eluting stent in the left circumflex artery (LCX). Therefore, we measured the coronary endothelial function (CEF) in the proximal to mid part of the left anterior descending artery (LAD). Upper panel: Quantitative coronary angiography (QCA) revealed the minimum lumen dimension (MLD) at baseline was 2.72 mm (arrow). Lower panel: After the maximum tolerance dose of ACh, the lumen dimension at the same part of the LAD (arrow) decreased to 1.54 mm. Accordingly, the CEF in this patient was 1.54/2.72 = 0.57

Therefore, we measured the CEF ratio at the proximal to midportion of the LAD. In this case, the QCA revealed MLD at baseline was 2.72 mm. After the maximum tolerance dose of ACh, the lumen dimension at the same part of the LAD decreased to 1.54 mm. Accordingly, the CEF ratio in this patient was 1.54/2.72 = 0.57.

2.6 | OCT evaluation

OCT images were acquired with a frequency domain OCT system (Abbott Vascular) in the nonstented LCA after evaluating the CEF. After the administration of intracoronary ISDN, a conventional angioplasty guidewire (0.014 inch) was advanced distal to the region of the CEF evaluation (proximal to the mid part of the nonstented LCA), then an OCT imaging catheter (Dragonfly, Abbott Vascular) was advanced over the guidewire beyond the above-mentioned region. During the imaging acquisition, blood was displaced by injection of contrast media. The images were calibrated by an automated adjustment of the Z-offset and the automated pullback was set at 18 or 36 mm/s.

OCT is a high-resolution intravascular imaging modality and provides a detailed assessment of the coronary vessel wall including the calcium lesions and thin-cap fibroatheroma (TCFA). Using OCT, we evaluated the calcified plaque and TCFA in the LCA because the two types of lesions were a kind of advanced atherosclerosis and could produce bias of the ACh provocation test.[16,17] In the OCT imaging TCFA was defined as a lipid-rich plaque with a minimal fibrous cap thickness of <65 μm (Figure 3 left panel)[18] and calcified plaque was defined as a signal-poor or heterogeneous region with a sharply delineated border (Figure 3 right panel).[19]

2.7 | Comparison of various parameters between F and B groups

We compared the SUA, oxidative stress markers including the MDA-LDL and inflammation markers; hs-CRP and renal markers including creatinine, cystatin C and the eGFR and the endothelial function; CEF ratio and coronary atherosclerotic changes including the OCT detected TCFA and calcified plaque between the F group and B group. We calculated the rate of change of the above-mentioned serum and urinary parameters between the 8-month follow-up and before the stenting as follows: (each parameter at the 8-month follow-up − each parameter at baseline)/each parameter at baseline. We compared the baseline, 8-month follow-up, and the rate of change of each serum and urinary parameter between the two groups. In addition, to evaluate the CIN, we calculated the rate of change of serum creatinine level between the 2-day after and before the stenting as follows: (creatinine level at 2 days after stenting − creatinine level at baseline)/creatinine level at baseline as 2-day % creatinine. Then, we compared 2-day % creatinine data between F and B groups. We also compared the incidence of traditional coronary risk factors including hypertension, dyslipidemia, diabetes mellitus (DM), and smoking between the two groups. Hypertension was identified in the patients whose systolic blood pressure was ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg, and/or the use of antihypertensive drugs; dyslipidemia was identified in patients treated with anticholesterolemic agents or whose serum low-density lipoprotein cholesterol level was ≥140 mg/dl; DM was identified as a fasting glucose level >126 md/dl and/or nonfasting glucose level >200 mg/dl, and/or the use of insulin or oral antihyperglycemic drugs.[20] In addition, we compared the medications including antiplatelet agents, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, β blockers, calcium channel blockers, and statins, the infusion volume of saline before and after PCI, and the amount of contrast media during PCI between the two groups.

Finally, we evaluated the protection of CEF, CIN, and renal function as the clinical outcomes. We compared CEF ratio as the protection of CEF, 2-day % creatinine as the protection of CIN, and % creatinine, eGFR, and cystatin C as the protection of the renal function between F group and B group.

2.8 | Statistical analysis

JMP 14 statistical software (SAS Institute Inc.) was used for the statistical analysis. Continuous parameters were expressed as median (interquartile range). Two-group comparisons were analyzed by the Mann–Whitney *U* test. Categorical data were expressed as counts

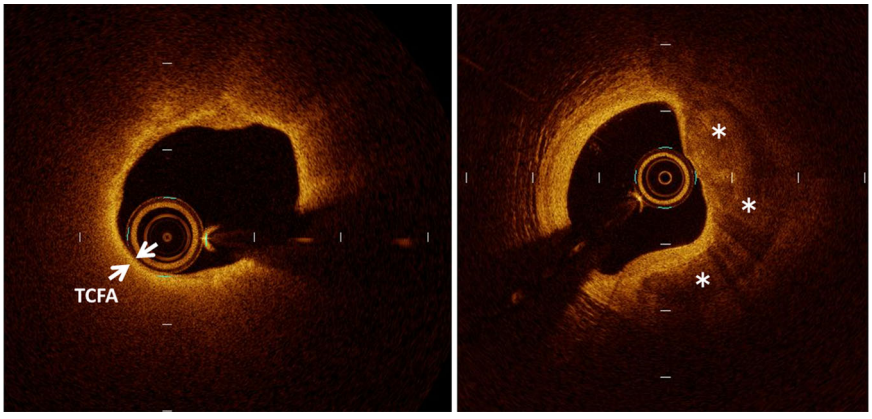

FIGURE 3 Left panel: optical coherence tomography (OCT) image showing a thin-cap fibroatheroma (TCFA) (arrow). Right panel: OCT image showing a calcified plaque (asterisk)

(percentages) and were compared using the Fisher test. A Wilcoxon signed-rank test was used for the comparison of the pre- and postdata. A p value of <0.05 was considered statistically significant.

3 | RESULTS

3.1 | Comparison of clinical characteristics, serum, and urinary markers at baseline between two groups

The F group consisted of 11 patients and B group of 10. In the F group, 45.5% of the patients received 20 mg and 54.5% received 40 mg febuxostat daily. As shown in Table 1, there were no significant differences in the age and incidence of major coronary risk factors including hypertension, dyslipidemia, DM, and smoking and the incidence of LAD stenting between the F and B groups. In addition, the SUA, oxidative stress markers including the MDA-LDL and 8-OHdG, inflammation markers; hs-CRP, renal markers including the creatinine, cystatin C and eGFR at baseline, medications, the infusion volume of saline before and after PCI, and amount of contrast media did not exhibit any significant differences between the two groups.

TABLE 1 Patient clinical characteristics

	F group (n = 11)	B group (n = 10)	p Value
Age	72 (67, 75)	71 (68, 73)	0.55
Hypertension (%)	90.9	80.0	0.59
Dyslipidemia (%)	72.7	40.0	0.66
Diabetes mellitus (%)	27.3	20.0	0.7
Smoking (%)	63.6	60.0	0.86
SUA (mg/dl)	7.0 (6.2, 8.9)	6.7 (6.1, 6.9)	0.16
8-OHdG (ng/ml)	8.0 (6.5, 14.5)	10.5 (8.9, 12.8)	0.41
MDA-LDL (U/l)	93 (71, 108)	91 (62, 98)	0.51
hs-CRP (mg/dl)	0.07 (0.06, 0.14)	0.08 (0.05, 0.21)	0.60
Creatinine (mg/dl)	1.0 (0.9, 1.1)	0.9 (0.8, 1.0)	0.38
Cystatin C (mg/l)	0.90 (0.85, 1.01)	0.90 (0.81, 0.92)	0.20
eGFR (ml/min/1.73 m^2)	60.0 (56.9, 63.2)	67.2 (58.2, 73.2)	0.18
Stent for LAD (%)	90.9	100	0.33
Antiplatelet agents (%)	100	100	-
ACEI/ARB (%)	72.7	80.0	0.67
β blocker (%)	54.5	50.0	0.83
CCB (%)	54.5	40.0	0.67
Statin (%)	90.9	90.0	0.94
Saline volume before PCI (ml)	250 (0, 875)	0 (0, 1000)	0.77
Saline volume after PCI (ml)	1000 (1000, 1375)	1000 (500, 1000)	0.55
Contrast media (ml)	100 (950, 123)	100 (100, 104)	0.15

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; eGFR, estimated glomerular filtration rate; hs-CRP, high sensitive C-reactive protein; 8-OhdG, 8-Hydroxy-2′-deoxyguanosine LAD, left anterior descending artery; MDA-LDL, low-density lipoprotein; PCI, percutaneous coronary intervention; SUA, serum uric acid.

3.2 | Medical effects on SUA, oxidant stress, and inflammation

In both groups, SUA (F group: 7.6 ± 1.7 vs. 5.5 ± 1.5 mg/dl, p = 0.02 and B group: 6.7 ± 0.7 vs. 4.4 ± 1.7 mg/dl, p < 0.01) and 8-OHdG (F group: 9.7 ± 4.5 vs. 8.0 ± 3.8 ng/ml, p < 0.001 and B group: 11.1 ± 3.0 vs. 9.0 ± 3.0 ng/ml, p = 0.003) were significantly reduced over the 8 months, but the other parameters did not show any significant differences during the 8 months. At the 8-month follow-up, there were no significant differences in the SUA, oxidant stress makers including the MDA-LDL and 8-OHdG, and hs-CRP as an inflammation marker between the two groups (Table 2). Regarding the incidence of the change in each parameter, there were also no significant differences between the two groups.

No gout arthritis occurred during the study period in both groups.

3.3 | Medical effects on CEF

There were no significant differences in the CEF ratio between the F group and the B group (Table 2). In addition, OCT revealed the incidence of TCFA and the calcified plaque were similar between the two groups.

3.4 | Medical protection of renal function including CIN

The rate of change in the eGFR was significantly lower in the F group than B group, whereas there was no significant difference in the 8-month follow-up eGFR between the two groups (Table 2). Regarding creatinine and cystatin C, there were no significant differences in the 8-month follow-up and rate of the change of cystatin C between the two groups. On the CIN, the rate of change between baseline and 2-day after in the creatinine (2-day % creatinine) tended to be more worsening in the B group than F group (p = 0.05), but the difference did not reach the statistical significance. As previously mentioned, there were no significant differences in the amount of saline and contrast media between the two groups.

4 | DISCUSSION

The main findings of the present study were that in the hyperuricemic patients with CAD, an 8 month-term inhibition of XO by febuxostat did not protect against an impaired CEF but could have

TABLE 2 Comparison of parameters between F and B Groups

	F group ($n = 11$)	B group ($n = 10$)	p Value
2-day creatinine (mg/dl)	1.1 (0.9, 1.3)	1.3 (1.2, 1.4)	0.11
8-month SUA (mg/dl)	6.0 (4.7, 6.3)	4.7 (2.6, 6.0)	0.12
8-month 8-OHdG(ng/ml)	7.3 (5.8, 11.0)	9.5(6.1, 11.5)	0.54
8-month MDA-LDL (U/l)	92.0 (83.0, 102.0)	90.0 (72.5, 99.3)	0.95
8 month hs-CRP (mg/dl)	0.05 (0.05, 0.10)	0.09 (0.07, 0.12)	0.78
8-month eGFR (ml/min/1.73m^2)	52.0 (50.0, 63.7)	50.0 (47.8, 54.5)	0.50
8-month Creatinine (mg/dl)	1.0 (1.0, 1.2)	1.0 (0.8, 13)	0.76
8-month Cystatin C (mg/l)	0.98 (0.86, 1.05)	0.86 (0.79, 0.94)	0.95
2-day % Creatinine	0.08 (−0.03, 0.29)	0.36 (0.16, 0.51)	0.05
% SUA	−0.28 (−0.39, −0.16)	−0.31 (−0.59, −0.12)	0.51
% 8-OHdG	−0.14 (−0.27, −0.11)	−0.15 (−0.37, −0.06)	0.69
% MDA-LDL	−0.10 (−0.20, 0.12)	−0.10 (−0.12, 0.36)	0.74
% hs-CRP	−0.14 (−0.45, 0.64)	−0.05 (−0.41, 0.28)	0.89
% Creatinine	0.07 (−0.05, 0.12)	−0.01 (−0.07, 0.18)	0.89
% eGFR	0 (−0.13, 0.06)	−0.24 (−0.32, −0.14)	0.04
% Cystatin C	−0.02 (−0.07, 0.12)	−0.02 (−0.03, 0.01)	0.98
CEF ratio	0.85 (0.62, 0.95)	0.95 (0.85, 0.96)	0.36
OCT TCFA (%)	0	0	-
OCT calcified plaque (%)	27.2	20.0	0.92

Abbreviations: OCT, optical coherence tomography. The other abbreviations are the same as in Table 1.

more favorable effects on protecting the renal function including CIN as compared to benzbromaron, a non-XO inhibitor.

4.1 | Effect on CEF

Oxidative stress and endothelial dysfunction are two inter-related conditions commonly seen in patients with cardiovascular risk factors.[21] Endothelial dysfunction, once it develops, is an important step in the progression of atherosclerosis,[22] and it has an important prognostic value for cardiovascular events in patients with CAD.[23] There have been many reports about the favorable effects of allopurinol, an established XO inhibitor, on the endothelial function using FMD.[21] However, there have been few reports on the effect of XO inhibitors on the CEF using an ACh provocation test, which can directly evaluate the CEF. Certainly, FMD is a reliable method to evaluate the endothelial function of the brachial artery or peripheral artery, but not to directly evaluate the CEF even if the FMD is reported to be well correlated with the CEF.[24] Previously, we reported that SUA is significantly correlated with VSA, which is an early step in coronary atherosclerosis, using 441 ACh provocation tests.[25] Moreover, Watanabe et al. reported that the XO activity is significantly associated with VSA.[26] In addition, it has been reported that the effect of XO inhibition is significantly higher with febuxostat than allopurinol.[27] Therefore, we speculated we could obtain favorable effects of SUA-lowering agents, especially febuxostat, on the CEF by using an ACh provocation test in this study. However, our results revealed no favorable effects of either febuxostat or benzbromarone on the CEF using the ACh provocation test even if both medications could reduce the serum SUA levels and 8-OHdG level. Additionally, in our study, febuxostat had no effect on one of the oxidative stress biomarkers, the MDA-LDL. The reason why our data failed to show any favorable effects of febuxostat on the CEF and MDA-LDL may be partially explained as follows: our study patients consisted of patients with advanced coronary atherosclerosis who were implanted with DESs. In the many previous reports, which showed the favorable effects of allopurinol and febuxostat on the FMD and oxidant stress biomarkers, the study patients consisted of early atherosclerosis patients including hypertension and VSA.[26,28] In addition, traditional coronary risk factors including hypertension, hyperdyslipidemia, and DM have been reported to be strongly correlated with the CEF and oxidative stress biomarkers.[29,30] Because the incidence of the traditional coronary risk factors was high in our study (Table 1), only a reduction in the SUA could not have had a significant effect on the CEF and oxidative stress biomarkers. Therefore, we think SUA-lowering agents, especially XO inhibitors, may be useful for early coronary atherosclerotic disease including VSA but not for advanced coronary

atherosclerosis disease including patients with stent implantations and multitraditional coronary risk factors as in our study population. Recently, Hays et al. have also reported that febuxostat does not significantly improve impaired CEF measured by magnetic resonance imaging in patients with stable CAD,[31] which may support our data. Other large-scaled clinical trials also have shown the non-beneficial effects of XO inhibitors, especially febuxostat, on cardiovascular events.[4–6]

4.2 | Effect on renal protection including CIN

Large-scaled clinical trials including the FEATHER and FREED trials have shown that febuxostat has a renoprotective effect, which might support our data.[4,5] Because all patients in this study underwent PCI and showed normal or mildly reduced renal function before PCI, our data regarding renal function reflected partially CIN. CIN is an important adverse reaction following PCI including stent implantations, which are associated with prolonged hospitalization and increased mortality.[32] The precise mechanism leading to CIN has not been fully elucidated. One of the possible mechanisms of CIN is that reactive oxygen species linked with the introduction of a contrast agent can contribute to the progression of CIN.[33] Reactive oxygen species may have both direct and indirect roles in the cortical and medullary microcirculation.[34] Accordingly, theoretically, XO inhibitors can partially protect CIN. Indeed, our data suggested that febuxostat, one of the established XO inhibitors, could show the tendency of renoprotection at 2 days after the PCI and could have favorable effects on the protection of the deterioration in the eGFR at 8-months after the PCI, whereas the amounts of saline and contrast media were similar between the two groups. Moreover, recent reports have shown elevated SUA is an independent risk factors for CIN.[35,36] Therefore, lowering SUA itself may prevent CIN. Accordingly, the two mechanisms including XO inhibitor and lowering SUA may partially explain the favorable effect of febuxostat on CIN.

4.3 | Different effects of febuxostat on CEF and renal function

The reason for the different effects of febuxostat on the CEF and renal protection in our study was unclear. However, the FEATHER study also reported that febuxostat did not have any cardiovascular protection, but did not aggravate renal function.[4] The FREED study revealed that febuxostat lowered the SUA and delayed the progression of the renal dysfunction, but did not decrease the cardiovascular events. There were many other studies that showed favorable effects of SUA-lowering agents that acted as an XO inhibitor on the renal function,[37] but there were few reports regarding the beneficial effects of an XO inhibitor on CAD.[38]

The reason for the discrepancy in the XO inhibitor effects on CAD and the renal function including CIN in this study is obscure, but the possible mechanism is as follows: the impact on the endothelial function may be more strongly correlated with the renal function than CAD because the renal function is dependent on medullary microcirculation, which is affected by oxidant stress,[33] but CAD is dependent on epicardial coronary atherosclerosis, which is a feature of advanced atherosclerosis as severe coronary artery stenosis and is not already affected by the endothelial dysfunction which is a feature of early atherosclerosis. In addition, in this study, the favorable effects on renal function by febuxostat may include the possible protection of CIN by XO inhibitor. The CEF is like that during the early stage of CAD[39] and even if the XO inhibitor has a beneficial effect on the CEF, it cannot affect advanced coronary atherosclerosis as in our study patients. In addition, because traditional risk factors including hypertension, dyslipidemia, and DM are strongly correlated with the CEF,[29,30] SUA-lowering agents including XO inhibitors did not have any effect on the CEF in our study patients who had multiple coronary risk factors. The recent PRIZE study has also revealed that febuxostat might be effective for attenuating earlier progression of carotid atherosclerosis, suggesting a limited role of febuxostat on the development of atherosclerosis[40] and this may partly support our findings.

4.4 | Limitations

This study has several limitations. First, this is a single-center study with small sample size. However, our study is the first study to evaluate the effect of febuxostat and benzobromarone on CEF directly by ACh provocation test. Therefore, we believe this data is valuable. Second, the final doses of febuxostat were different and lower than expected, with approximately half of the study patients on 20 mg daily of febuxostat. However, because it has been reported that 20 mg of febuxostat is effective for renal protection[41] and reduction of oxidant stress,[42] final doses of febuxostat might not strongly affect our data. Finally, we enrolled asymptomatic hyperuricemic patients as in the recent randomized trials in Japanese.[4,5,40] Accordingly, this data may be different from the studies performed in regions other than Japan and may not be applied to symptomatic hyperuricemia.

5 | CONCLUSION

Febuxostat can protect against renal dysfunction including CIN but not the CEF as compared to benzbromarone in hyperuricemic patients with CAD, but, both medications have similar SUA-lowering effects.

ACKNOWLEDGMENTS

The authors thank Mr. John Martin for his linguistic assistance with this manuscript. The work was funded by Teijin Pharma, Limited, Japan. The funder of this study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

ETHICS STATEMENT

The lead author confirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

AUTHOR CONTRIBUTIONS

Conceptualization: Masami Nishino, Yasuyuki Egami, and Jun Tanouchi. *Formal analysis*: Masami Nishino and Hitoshi Nakamura. *Funding acquisition*: Masami Nishino. *Investigation*: Kohei Ukita and Akito Kawamura. *Methodology*: Yutaka Matsuhiro and Koji Yasumoto. *Supervision*: Masaki Tsuda, Akihiro Tanaka, and Naotaka Okamoto. *Validation*: Yasuharu Matsunaga-Lee and Masamichi Yano. *Visualization*: Ryu Shutta. *Writing—original draft preparation*: Masami Nishino. *Writing—review and editing*: Masami Nishino, Ryu Shutta, and Jun Tanouchi. All authors have read and approved the final version of the manuscript. Masami Nishino had full access to all the data in this study and acts as guarantor for the integrity of the data and the accuracy of the data analysis.

DATA AVAILABILITY STATEMENT

The datasets used and analyzed during the current study are available from the corresponding author on request.

ORCID

Masami Nishino http://orcid.org/0000-0003-0309-7023

REFERENCES

1. Bose B, Badve SV, Hiremath SS, et al. Effects of uric acid-lowering therapy on renal outcomes: a systematic review and meta-analysis. *Nephrol Dial Transplant*. 2014;29:406-413.
2. Li M, Hu X, Fan Y, et al. Hyperuricemia and the risk for coronary heart disease morbidity and mortality a systematic review and dose-response meta-analysis. *Sci Rep*. 2016;6:19520.
3. Doehner W, Springer J, Landmesser U, Struthers AD, Anker SD. Uric acid in chronic heart failure—current pathophysiological concepts. *Eur J Heart Fail*. 2008;10:1269-1270.
4. Kimura K, Hosoya T, Uchida S, et al. Febuxostat therapy for patients with Stage 3 CKD and asymptomatic hyperuricemia: a randomized trial. *Am J Kidney Dis*. 2018;72:798-810.
5. Kojima S, Matsui K, Hiramitsu S, et al. Febuxostat for cerebral and cardiorenovascular events prevention study. *Eur Heart J*. 2019;40:1778-1786.
6. White WB, Saag KG, Becker MA, et al. Cardiovascular safety of febuxostat or allopurinol in patients with gout. *N Engl J Med*. 2018;378:1200-1210.
7. Cicero AFG, Pirro M, Watts GF, Mikhailidis DP, Banach M, Sahebkar A. Effects of allopurinol on endothelial function: a systematic review and meta-analysis of randomized placebo-controlled trials. *Drugs*. 2018;78:99-109.
8. Doehner W, Schoene N, Rauchhaus M, et al. Effects of xanthine oxidase inhibition with allopurinol on endothelial function and peripheral blood flow in hyperuricemic patients with chronic heart failure: results from 2 placebo-controlled studies. *Circulation*. 2002;105:2619-2624.
9. Struthers AD, Donnan PT, Lindsay P, McNaughton D, Broomhall J, MacDonald TM. Effect of allopurinol on mortality and hospitalisations in chronic heart failure: a retrospective cohort study. *Heart*. 2002;87:229-234.
10. Doehner W, von Haehling S, Anker SD. Uric acid in CHF: marker or player in a metabolic disease? *Int J Cardiol*. 2007;115:156-158.
11. Sueda S, Kohno H, Ochi T, Uraoka T. Overview of the acetylcholine spasm provocation test. *Clin Cardiol*. 2015;38:430-438.
12. Torgerson DJ, Roberts C. Understanding controlled trials: randomisation methods: concealment. *BMJ*. 1999;319:375-376.
13. Matsuo S, Imai E, Horio M, et al. Revised equations for estimated GFR from serum creatinine in Japan. *Am J Kidney Dis*. 2009;53:982-992.
14. Jabara R, Gadesam RR, Pendyala LK, et al. Impact of the definition utilized on the rate of contrast-induced nephropathy in percutaneous coronary intervention. *Am J Cardiol*. 2009;103:1657-1662.
15. Mitsutake Y, Ueno T, Yokoyama S, et al. Coronary endothelial dysfunction distal to stent of first-generation drug-eluting stents. *JACC Cardiovasc Interv*. 2012;5:966-973.
16. Matsuzawa Y, Hibi K, Saka K, et al. Association of endothelial function with thin-cap fibroatheroma as assessed by optical coherence tomography in patients with acute coronary syndromes. *Ther Clin Risk Manag*. 2019;15:285-291.
17. Yao Y, Jumabay M, Ly A, Radparvar M, Cubberly MR, Boström KI. A role for the endothelium in vascular calcification. *Circ Res*. 2013;113:495-504.
18. Jia H, Abtahian F, Aguirre AD, et al. In vivo diagnosis of plaque erosion and calcified nodule in patients with acute coronary syndrome by intravascular optical coherence tomography. *J Am Coll Cardiol*. 2013;62:1748-1758.
19. Yabushita H, Bouma BE, Houser SL, et al. Characterization of human atherosclerosis by optical coherence tomography. *Circulation*. 2002;106:1640-1645.
20. Bhatt DL. International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. *JAMA*. 2006;295:180-189.
21. Alem MM. Allopurinol and endothelial function: a systematic review with meta-analysis of randomized controlled trials. *Cardiovasc Ther*. 2018;36:e12432.
22. Celermajer DS, Sorensen KE, Gooch VM, et al. Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis. *Lancet*. 1992;340:1111-1115.
23. Heitzer T, Schlinzig T, Krohn K, Meinertz T, Münzel T. Endothelial dysfunction, oxidative stress, and risk of cardiovascular events in patients with coronary artery disease. *Circulation*. 2001;104:2673-2678.
24. Flammer AJ, Anderson T, Celermajer DS, et al. The assessment of endothelial function: from research into clinical practice. *Circulation*. 2012;126:753-767.
25. Nishino M, Mori N, Yoshimura T, et al. Higher serum uric acid and lipoprotein(a) are correlated with coronary spasm. *Heart Vessels*. 2014;29:186-190.
26. Watanabe K, Shishido T, Otaki Y, et al. Increased plasma xanthine oxidoreductase activity deteriorates coronary artery spasm. *Heart Vessels*. 2019;34:1-8.
27. Nakamura T, Murase T, Nampei M, et al. Effects of topiroxostat and febuxostat on urinary albumin excretion and plasma xanthine oxidoreductase activity in db/db mice. *Eur J Pharmacol*. 2016;780:224-231.
28. Oyama J, Tanaka A, Sato Y, et al. Rationale and design of a multicenter randomized study for evaluating vascular function under uric acid control using the xanthine oxidase inhibitor, febuxostat: the PRIZE study. *Cardiovasc Diabetol*. 2016;15:87.
29. Calles-Escandon J, Cipolla M. Diabetes and endothelial dysfunction: a clinical perspective. *Endocr Rev*. 2001;22:36-52.

30. Touyz RM, Rios FJ, Alves-Lopes R, Neves KB, Camargo LL, Montezano AC. Oxidative stress: a unifying paradigm in hypertension. *Can J Cardiol*. 2020;36:659-670.
31. Hays AG, Iantorno M, Schar M, et al. The influence of febuxostat on coronary artery endothelial dysfunction in patients with coronary artery disease: a phase 4 randomized, placebo-controlled, double-blind, crossover trial. *Am Heart J*. 2018;197:85-93.
32. McCullough PA, Sandberg KR. Epidemiology of contrast-induced nephropathy. *Rev Cardiovasc Med*. 2003;4(Suppl 5):S3-S9.
33. Heyman SN, Rosen S, Rosenberger C. Renal parenchymal hypoxia, hypoxia adaptation, and the pathogenesis of radiocontrast nephropathy. *Clin J Am Soc Nephrol*. 2008;3:288-296.
34. Xu R, Tao A, Bai Y, Deng Y, Chen G. Effectiveness of N-acetylcysteine for the prevention of contrast-induced nephropathy: a systematic review and meta-analysis of randomized controlled trials. *J Am Heart Assoc*. 2016;5:e003968.
35. Mendi MA, Afsar B, Oksuz F, et al. Uric acid is a useful tool to predict contrast-induced nephropathy. *Angiology*. 2017;68:627-632.
36. Kanbay M, Solak Y, Afsar B, et al. Serum uric acid and risk for acute kidney injury following contrast. *Angiology*. 2017;68:132-144.
37. Tanaka K, Nakayama M, Kanno M, et al. Renoprotective effects of febuxostat in hyperuricemic patients with chronic kidney disease: a parallel-group, randomized, controlled trial. *Clin Exp Nephrol*. 2015;19:1044-1053.
38. Noman A, Ang DS, Ogston S, Lang CC, Struthers AD. Effect of high-dose allopurinol on exercise in patients with chronic stable angina: a randomised, placebo controlled crossover trial. *Lancet*. 2010;375:2161-2167.
39. Raitakari OT, Celermajer DS. Flow-mediated dilatation. *Br J Clin Pharmacol*. 2000;50:397-404.
40. Tanaka A, Taguchi I, Teragawa H, et al. Febuxostat does not delay progression of carotid atherosclerosis in patients with asymptomatic hyperuricemia: a randomized, controlled trial. *PLOS Med*. 2020;17:e1003095.
41. Ito H, Antoku S, Abe M, et al. Comparison of the Renoprotective effect of febuxostat for the treatment of hyperuricemia between patients with and without type 2 diabetes mellitus: a retrospective observational study. *Intern Med*. 2016;55:3247-3256.
42. Fukui T, Maruyama M, Yamauchi K, Yoshitaka S, Yasuda T, Abe Y. Effects of febuxostat on oxidative stress. *Clin Ther*. 2015;37:1396-1401.

How to cite this article: Nishino M, Egami Y, Nakamura H, et al. Prospective randomized comparison of effect on coronary endothelial and renal function between febuxostat and benzbromarone in hyperuricemic patients with coronary artery disease: EFEF study. *Health Sci. Rep*. 2022;5:e563. doi:10.1002/hsr2.563